REMARKS

The remainder of this Reply is set forth under appropriate subheadings for the convenience of the Examiner.

Amendment to the Claims

Claim 1 was amended to more clearly define Applicant's claimed invention.

Amendments to the Specification

The specification was amended at page 5, line 13 to correct a typographical in the abbreviation for glomerulonephritis. Support for this amendment is found in the Figure.

The specification was amended at page 8, lines 13 and 15 to correct a typographical error in the designation of oxygen.

The specification was amended at page 17, line 28 to correct a self-evident typographical error in the description of the glomerular filtration rate. Support for this amendment is found in the specification, for example, at page 16, lines 17-20.

Table 1 was amended to correct a typographical error in the abbreviation of Henoch-Schonlein Purpura. Support for this amendment is found in Table 1, line 39.

No new matter is added in the amendments to the specification. Entry is requested.

Applicant's Claimed Invention

Applicant's invention, as set forth in Claims 1-14, is directed to a method of treating a progressive kidney disease in a human, comprising the step of administering an iron chelator to the human. The progressive kidney disease can be at least one member selected from the group consisting of diabetic nephropathy, primary glomerulonephritis and secondary glomerulonephritis.

Advantages of Applicant's Claimed Invention

As discussed on page 7, lines 14-23, a progressive kidney disease can lead to loss of renal function and, ultimately, end-stage renal disease. A human with a progressive kidney disease has

functioning kidneys, albeit with diminished renal function compared to a human without a progressive kidney disease. The progression of the kidney disease can be determined, for example, by assessing an increase in protein in urine obtained from the human. As discussed on page 1, line 13 through page 2, line 3 of the specification, currently available treatments for kidney diseases, in particular progressive kidney diseases, include the use of steroids, alkylating agents and cyclosporine, which are often associated with adverse side effects, such as, cellular and systemic toxicity. An advantage of Applicant's claimed invention is the treatment of a progressive kidney disease to prevent further progression of the kidney disease to, for example, end-stage renal disease, by chelating iron that is causing damage to the kidney without the use of agents that result in adverse side-effects.

Rejection of Claim 3 Under 35 U.S.C. § 112, Second Paragraph

Claim 3 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner stated that no objective criterion is provided in the specification or claim to appraise one of skill in the art of any meaning of "essentially constant" and, thus, the metes and bounds of this term is unclear.

Page 15, lines 7-9 of the specification define the phrase "essentially constant" as:

> "Essentially constant" (also referred to herein as "an essentially constant value" or stabilized) refers to a catalytic iron content in the urine that remains about the same value over time (e.g., days, weeks, months or years).

Thus, the phrase "essentially constant" is clear. Therefore, Claim 3 meets the requirement of 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1-3, 6, 7, and 9-14 Under 35 U.S.C. § 102(b)

Claims 1-3, 6, 7, and 9-14 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,684,482, issued to Green, D.E. (hereinafter "Green"), as evidenced by U.S. Patent Nos: 6,206,849, issued to Martin, G. S., *et al.* (hereinafter "Martin"); 6,383,817, issued to

Schwartz, G.G. (hereinafter "Schwartz"); 6,706,287, issued to Ranganathan, N. *et al.* (hereinafter "Ranganathan"); and Akbarov, A.B. *et al.,* WO 00/54784 (hereinafter "Akbarov"). The Examiner stated that Green teaches a method of orally administering an iron chelator, such as deferoxamine, to treat kidney-damaged patients undergoing renal dialysis. The Examiner also stated that Martin teaches that patients undergoing renal dialysis have kidney damage associated with end-stage progressive kidney disease and deferoxamine would inherently halt the progression of the kidney disease and/or reduce the severity of the progressive kidney disease and/or reduce the rate of loss of renal function when administered to patients undergoing dialysis due to kidney damage associated with end-stage kidney disease. In addition, the Examiner stated that Schwartz teaches that proteinurea is indicative of kidney damage and/or failure, Ranganathan teaches that an increase in serum creatinine is indicative of kidney failure and/or kidney damage and Akbarov teaches that treating progressive kidney damage increases the glomerular filtration rate.

Green describes administering acyl derivatives of deferoxamine for treatment of iron overload diseases including iron overload diseases in humans undergoing renal dialysis. In column 1, lines 9-33, Green states:

> Iron overload diseases include thalassemia major, sideroachrestic anemia, Blackfan-Diamond anemia, aplastic anemia, sickle cell amenia, other hemolytic anemias, and a number of other diseases and conditions in which hemosiderosis (a focal or general increase in tissue iron stores without associated tissue damage) occurs. One type of hemosiderosis occurs in most patients after multiple blood transfusions have occurred. Another type of hemosiderosis occurs as the result of the treatment of an anemia found in kidney damaged patients where dialysis is used to remove toxic wastes.

Green does not teach, expressly or inherently, a method for treating a progressive kidney disease in a human by administering an iron chelator to the human, which is the subject matter of Applicant's claimed invention, as set forth in Claims 1-3, 6, 7 and 9-14.

As noted by the Examiner, Green teaches the use of acyl derivatives of deferoxamine for the treatment of humans who are undergoing renal dialysis. End-stage renal disease is the end

result of a progressive kidney disease. In end-stage renal disease, the kidney disease has advanced to a degree that requires dialysis or kidney transplant.

As discussed above, Applicant's claimed invention, as set forth in Claims 1-3, 6, 7 and 9-14, is directed to a method of treating a progressive kidney disease in a human by administering an iron chelator to the human. On page 6, lines 16-17 of the specification, progressive kidney disease is defined as:

> any disease of the kidney that over time (e.g., days, weeks, months, years) leads to a loss of renal function.

Renal function, in turn, is defined on page 6, lines 18-23 of the specification as:

> a physiological property of the kidney, such as the ability to retain protein thereby preventing proteinuria (e.g., urinary creatinine, the excretion of protein in an amount greater than about 0.15g/24 hours). Renal function can be assessed, for example, by glomerular filtration rate (e.g., creatinine clearance), excretion of protein in urine, blood urea nitrogen, serum or plasma creatinine, or any combination thereof.

Diseases of the kidney as a consequence to iron overload are not necessarily a progressive kidney disease treated by Applicant's claimed method. In particular, page 7, lines 14-22 of the specification states:

> A progressive kidney disease of the invention is not a disease of the kidney that results from exogenous iron overload as a result of, for example, repeated blood transfusions in diseases such as thalessemia or sickle cell anemia.

Humans with a progressive kidney disease have kidneys that can function, albeit at a reduced level compared to an individual without a progressive kidney disease. Dialysis or renal transplantation is not required until the human reaches end-stage renal disease. If a progressive kidney disease is not treated, it can result in end-stage renal disease, as stated on page 7, lines 14-15 of the specification:

> A progressive kidney disease treated by the methods described herein includes any kidney disease that can, ultimately, lead to end-stage renal disease.

As stated in the Medline Plus Medical Dictionary, www.nlm.nih.gov/medlineplus/ency/article/000500.htm, attached to this Reply as an Exhibit, end stage renal disease is:

> a complete or near complete failure of the kidneys to function to excrete wastes, concentrate urine and regulate electrolytes ... End-stage kidney disease occurs when the kidneys are no longer able to function at a level necessary for day-to-day life. It usually occurs as chronic renal failure progresses to the point where kidney function is less than 10% of baseline. At this point, the kidney function is so low that without dialysis or kidney transplantation, complications are multiple and severe, and death will occur from accumulation of fluids and waste products in the body.

End-stage renal disease requires dialysis or kidney transplantation.

There is no express teaching by Green of a method for treating a human with a progressive kidney disease by administering an iron chelator. Humans having iron overload conditions, such as thalassemia major, sideroachrestic anemic, Blackfan-Diamond anemia, aplastic anemia, sickle cell anemia, nemolytic anemias and nemosiderosis, which are described by Green and treated by the aryl derivatives of Green, do not necessarily have a progressive kidney disease. Therefore, Green also does not inherently teach a method for treating a human having a progressive kidney disease by administering an iron chelator. Thus, Green does not anticipate Claims 1-3, 6, 7 and 9-14 and Applicant's claimed invention meets the requirements of 35 U.S.C. § 102(b).

Martin describes a multiple lumen catheter for insertion into a vein of a patient for haemodialysis treatment. In column 2, lines 22-27, Martin states:

> In the case of chronic renal impairment or failure, haemodialysis has to be carried out on a repetitive basis. For example, in end stage kidney disease where transplantation of kidneys is not possible or for medical reasons is contraindicated,

> the patient will have to be dialysed about 100 to 150 times per year.

There is no teaching, expressly or inherently, in Martin of a method for treating a human with a progressive kidney disease by administering an iron chelator. Martin does not teach the use of the iron chelators to treat any kidney disease. The only kidney disease Martin mentions is end-stage renal disease, which Martin teaches would require dialysis. As discussed above, end-stage renal disease is the end result of a progressive kidney disease. Therefore, Martin does not anticipate, expressly or inherently, Applicant's claimed invention nor does Martin evidence anticipation of Claims 1-3, 6, 7 and 9-14 by Green.

Schwartz, issued on May 7, 2002, claims the benefit of U.S. Application No: 60/173,760, filed December 30, 1999. The instant application is a divisional application of U.S. Application No: 09/553,496, filed April 20, 2000, which claims the benefit of U.S. Application No: 60/130,908, filed April 23, 1999. Schwartz is not prior art for the instant application. In addition, Schwartz teaches a method for screening for risk of pancreatic cancer in a subject by detecting the presence or absence of increased levels of cadmium in the subject. Schwartz teaches that retinol-binding protein (RBP) is a measure of low molecular weight proteinurea, which is increased by kidney damage, in particular, by exposure to cadmium. Schwartz further teaches that increased urinary RBP is a well studied measure of the effects of cadmium on the kidney and can serve as a surrogate marker for the effect of cadmium damage on the pancreas.

Schwartz does not teach, expressly or inherently, Applicant's claimed method for treating a progressive kidney disease by administering an iron chelator. Therefore, Schwartz does not anticipate Applicant's claimed invention, as set forth in Claims 1-3, 6, 7 and 9-14, because it is not prior art to the instant application and does not evidence anticipation by Green.

Ranganathnan, issued March 16, 2004, was filed May 15, 2001. As discussed above, the instant application claims the benefit of an application filed April 23, 1999. Ranganathnan is not prior art to the instant application. In addition, Ranganathnan teaches pharmaceutical compositions comprising a probiotic to restore the normal balance between beneficial bacteria and detrimental bacteria to remove excess urea-waste product of normal protein metabolism to reduce the burden on an ailing kidney and to remove ammonia to avert mental retardation and

related conditions. Ranganathan teach a decrease in glomerular filtration in kidney failure and the inability of the kidneys to maintain homeostasis of the blood under these conditions. Ranganathan teach that when a patient has mild kidney failure, with a serum creatinine level less than 400 μmol/L, the patient does not require renal replacement therapy and when serum creatinine level rise to 900 μmol/L, the patient needs routine dialysis or a kidney transplant to survive.

There is no express or inherent teaching in Ranganathan of a method to treat a progressive kidney disease by administering an iron chelator, which is the subject matter of Applicant's claimed invention, as set forth in Claims 1-3, 6, 7 and 9-14. Therefore, Ranganathan does not anticipate Applicant's claimed method because it is not prior art to the instant application and does not evidence anticipation of Claims 12 and 14 by Green.

Akbarov teaches a coordination compound comprising manganese, glutamic acid and vitamin C for the treatment of kidney disease.

Akbarov does not expressly or inherently teach a method for treating a progressive kidney disease in a human by administering an iron chelator. Therefore, Akbarov does not anticipate Applicant's claimed invention and does not evidence anticipation by Green.

There is no express or inherent teaching in Green, as evidenced by Martin, Schwartz, Ranganathan and Akbarov, of a method for treating a progressive kidney disease in a human by administering an iron chelator to the human. In addition, Schwartz and Ranganathan are not prior art to the instant application. Therefore, Green does not anticipate Claims 1-3, 6, 7 and 9-14 and Martin, Schwartz, Ranganathan and Akbarov do not evidence anticipation of Claims 1-3, 6, 7 and 9-14 by Green.

Rejection of Claims 4, 5 and 8 under 35 U.S.C. § 103

Claims 4, 5 and 8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Green, in further view of JP 405000949, by Mita, S., *et al.* (hereinafter "Mita"). The Examiner stated that it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention was made to have administered an iron chelator to a patient suffering from diabetic nephropathy because Green teaches administering an iron chelator to a patient with kidney damage and Mita teaches that diabetic nephropathy causes kidney failure and/or damage.

As discussed above, Green does not teach, expressly or inherently, a method for treating a progressive kidney disease in a human by administering an iron chelator to the human. As discussed above, Green teaches the use of acyl derivatives of deferoxamine to treat iron overload diseases, including accompanying conditions consequent to iron overload diseases that require renal dialysis.

Green does not teach, expressly or inherently, or suggest a method for treating a progressive kidney disease by administering an iron chelator in a range of between about 20 mg/kg body weight and about 150 mg/kg body weight of the human per day, which is the subject matter of Claim 4; in a human suffering from a progressive kidney disease selected from the group consisting of diabetic nephropathy, primary glomerulonephritis and secondary glomerulonephritis, which is the subject matter of Claim 5; or by administering the iron chelator to a human having a progressive kidney disease in multiple doses, which is the subject matter of Claim 8.

Mita describes the use of a benzothiazine derivative to treat kidney failure caused by nephritis, diabetic nephropathy, obstructive nephropathy and for preventing nephropathy and maintaining the function of a kidney after transplantation. The benzothiazine derivatives of Mita are not iron chelators.

Mita does not remedy the deficiencies of Green. In particular, Mita does not teach, expressly or inherently, or suggest a method for treating a progressive kidney disease by administering an iron chelator. Mita does not teach or suggest administering an iron chelator in a range of between about 20 mg/kg body weight and about 150 mg/kg body weight of the human per day, which is the subject matter of Claim 4; in a human suffering from a progressive kidney disease selected from the group consisting of diabetic nephropathy, primary glomerulonephritis and secondary glomerulonephritis, which is the subject matter of Claim 5; or by administering the iron chelator to a human having a progressive kidney disease in multiple doses, which is the subject matter of Claim 8.

Therefore, Applicant's claimed invention, as set forth in Claims 4, 5 and 8, meets the requirements of 35 U.S.C. §103 over Green, in view of Mita.

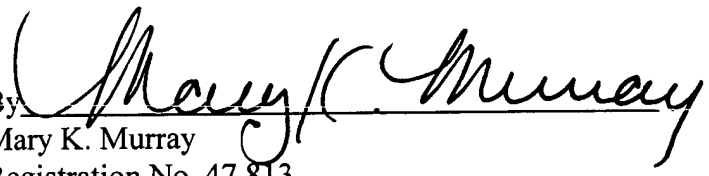
SUMMARY AND CONCLUSIONS

Claim 3 meets the requirements of 35 U.S.C. §112, second paragraph. Claims 1-3, 6, 7 and 9-14 meet the requirements of 35 U.S.C. §102(b) in view of Green, as evidenced by Martin, Schwartz, Ranganathan and Akbarov. Claims 4, 5 and 8 meet the requirements of 35 U.S.C. §103(a) over Green, in view of Mita. Therefore, Applicant respectfully requests reconsideration and allowance of the claims under consideration.

If the Examiner feels that a telephone conference would expedite prosecution of this application, he is invited to call Applicant's undersigned Attorney.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By 
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Medical Encyclopedia: End-stage kidney disease

URL of this page: http://www.nlm.nih.gov/medlineplus/ency/article/000500.htm

Alternative names

Renal failure - end stage; Kidney failure - end stage; ESRD

Definition

End-stage kidney disease is a complete or near complete failure of the kidneys to function to excrete wastes, concentrate urine, and regulate electrolytes. Also called End-stage renal disease (ESRD).

Causes, incidence, and risk factors

End-stage kidney disease occurs when the kidneys are no longer able to function at a level that is necessary for day to day life. It usually occurs as chronic renal failure progresses to the point where kidney function is less than 10% of baseline. At this point, the kidney function is so low that without dialysis or kidney transplantation, complications are multiple and severe, and death will occur from accumulation of fluids and waste products in the body.

In the United States, nearly 300,000 people are on long-term dialysis and more than 20,000 have a functioning transplanted kidney. The most common cause of ESRD in the US is diabetes. ESRD almost always follows chronic kidney failure, which may exist for 10 to 20 years or more before progression to ESRD.

Symptoms

- Unintentional weight loss
- Nausea or vomiting
- General ill feeling
- Fatigue
- Headache
- Frequent hiccups
- Generalized itching
- Greatly decreased urine output
- No urine output
- Easy bruising or bleeding
- May have blood in the vomit or stools
- Decreased alertness
    - drowsiness, somnolence, lethargy
    - confusion, delirium
    - coma
- Muscle twitching or cramps
- Seizures
- Increased skin pigmentation
- Skin may appear yellow or brown
- Nail abnormalities
- Decreased sensation in the hands, feet, or other areas

EXHIBIT

Signs and tests

The patient usually has a long history of chronic kidney failure, which has progressed. The person may have required dialysis to control chronic renal failure. The urine volume may decrease or urine production may stop totally. Signs of complications commonly are present.

- Creatinine and BUN levels are chronically high.
- Creatinine clearance is very low.

Treatment

Dialysis or kidney transplantation are the only treatments for ESRD. The physical condition of the person and other factors determines which of these is used for treatment. Other treatments of chronic kidney failure may continue but are ineffective without dialysis or transplantation.

Associated diseases that cause or result from chronic renal failure must be controlled. Hypertension, congestive heart failure, urinary tract infections, kidney stones, obstructions of the urinary tract, glomerulonephritis, and other disorders should be treated as appropriate.

Blood transfusions and medications such as iron and erythropoietin may be needed to control anemia. Fluids may be restricted to an amount nearly equal to the volume of urine produced.

Dietary restrictions may slow the build-up of wastes in the bloodstream and control associated symptoms such as nausea and vomiting. Restrictions include low protein in diet, with high carbohydrate levels to make up calories. Salt, potassium, phosphorus, and other electrolytes may be restricted.

Support Groups

For additional resources, see kidney disease support group.

Expectations (prognosis)

ESRD is fatal unless treated with dialysis or transplantation. Both of these treatments can have serious risks and consequences. The outcome varies and is unique to each individual.

Complications

- Pericarditis, cardiac tamponade
- Congestive heart failure
- Hypertension
- Platelet dysfunction
- Gastrointestinal loss of blood; duodenal or peptic ulcers
- Hemorrhage
- Anemia
- Hepatitis B, hepatitis C, liver failure
- Decreased functioning of white blood cells and immune system
- Infection
- Peripheral neuropathy
- Seizures
- Encephalopathy, nervous system damage, dementia
- Weakening of the bones, fractures, joint disorders
- Permanent skin pigmentation changes
- Skin dryness, itching/scratching with resultant skin infection
- Changes in glucose metabolism
- Changes in electrolyte levels
- Decreased libido, impotence
- Miscarriage, menstrual irregularities, infertility

Calling your health care provider

Go to the emergency room or call the local emergency number (such as 911) if symptoms indicating end-stage kidney disease have developed. Call your health care provider if known acute or chronic kidney failure persists or worsens.

Prevention

Treatment of chronic kidney failure may delay or prevent progression to ESRD. Some cases may not be preventable.

Update Date: 10/17/2003

Updated by: Irfan A. Agha, M.D., Department of Medicine, Renal Division, St. Louis University, St. Louis, MO. Review provided by VeriMed Healthcare Network.